EurJOC
European Journal of Organic Chemistry

Concept
doi.org/10.1002/ejoc.202400604

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

Synthetic Strategies and Applications of Fluorine-Containing Bridged Bicyclic Compounds

Simone Baldon,[a] Luca Dell'Amico,[a] and Sara Cuadros*[a]

Bridged bicyclic compounds (BBCs) have recently emerged as effective 3D-isosteres of planar aryl and heteroaryl rings. Current synthetic endeavours are devoted to accessing these complex structures bearing functionalities in different positions of the aliphatic rings. Of particular interest is the incorporation of F-containing motifs, since it allows the generation of isosteric units with improved physicochemical properties, including lipophilicity, water solubility, or oxidative resistance.

1. Introduction

The replacement of a functional group with its bioisostere counterpart is a commonly used strategy in drug optimization. This approach aims at enhancing the ADME (administration, distribution, metabolism and excretion) profiles of drug-candidates, while maintaining the key drug-target interactions unaltered.[1] In recent decades, bridged bicyclic compounds (BBCs) have emerged as powerful 3D-bioisosteres of planar arene rings, being bicyclo[1.1.1]pentanes (BCPs) one of the most popular bicyclic cores. These rigid, strained motifs can help in preventing undesirable intermolecular π-π stacking interactions, thereby leading to notable enhancements in properties such as water solubility.[2]

On the other hand, a well recognized strategy to improve the pharmacokinetic performance and potency of bioactive compounds is the incorporation of fluorine atoms or F-containing groups. Generally, this modification allows to reinforce the oxidation resistance of molecules, but also provides additional opportunities for multipolar F-protein interactions.[3] Several fluorinated groups have been successfully used as bioisosteric replacements for common functionalities. For instance, the $-CF_3$ and $-CF_2-$ groups have served as effective surrogates for carbonyl groups or oxygen atoms, among others.[4]

Given the inherent advantages of both bicyclic frameworks and F-containing groups in enhancing pharmaceutical properties, it is not surprising that the synthetic community have dedicated significant efforts to synthesize and study new classes of *hybrid 3D-isosteres* combining these two structural units. Early investigations into fluorinated BCPs date back to 1999, where Adcock, Savéant and coworkers determined oxidation potentials (E_p) and pKa values of different 1,3-subsituted BCPs **1** (Figure 1a).[5] Both set of data reflect how substituent electronic effects are effectively transmitted through the BCP ring system. An alternative avenue in the molecular design of 3D-scaffolds involves the installation of fluorine in the bridge positions of the bicycle, affording compounds that can exhibit a good balance between water solubility and lipophilicity (Figure 1b). For instance, Mykhailiuk and coworkers provided an interesting comparative analysis involving amides **2**–**4**, wherein the exchange of the benzene moiety in **2** with the *gem*-difluoro BCP motif **4** resulted in a considerable increase of its water solubility, while maintaining the lipophilicity of the parent molecule **2**.[6]

In addition to developing synthetic methods for constructing F-containing BBCs, significant efforts have also been dedicated to their application in replacing arene rings, aryl ether, or aryl ketone functionalities within known biologically molecules (Figure 1c). For example, the research groups of MacMillan, Dell'Amico or Zhang have successfully synthesized analogues of *leflunomide* **6**, a *leukotriene A_4 hydrolase inhibitor* **8**, and *adiporon* **10**, respectively, demonstrating enhanced physicochemical parameters compared to their parent arene compounds.[7–9]

In this Concept, we provide an overview of the latest methodologies employed in the synthesis of F-containing BBCs. The synthetic strategies have been systematically categorized based on the site of functionalization (*i.e.* bridge or bridgehead), and further delineated by the distinct F-containing motifs integrated into the byclic core. Finally, we discuss potential advancements in the field, addressing current synthetic challenges and outlining future directions for research.

2. Bridgehead Functionalization

2.1. Introduction of Fluorine and Fluoroalkyl Groups

In 2015, Adsool and Goh developed a one-step protocol to access the fluorinated derivative **13** from the corresponding dicarboxylic acid **11** (Figure 2).[10] The methodology is based on a decarboxylative radical fluorination process, using Selectfluor® **12** as the fluorinating agent together with $AgNO_3$ serving as a catalyst. This procedure is one of the first examples of an efficient scalable route to the mono-fluorinated product

[a] *S. Baldon, L. Dell'Amico, S. Cuadros*
Department of Chemical Sciences, University of Padova, Via Francesco Marzolo 1, 35131 Padova, Italy
E-mail: sara.cuadroshuertas@unipd.it

Concept
doi.org/10.1002/ejoc.202400604

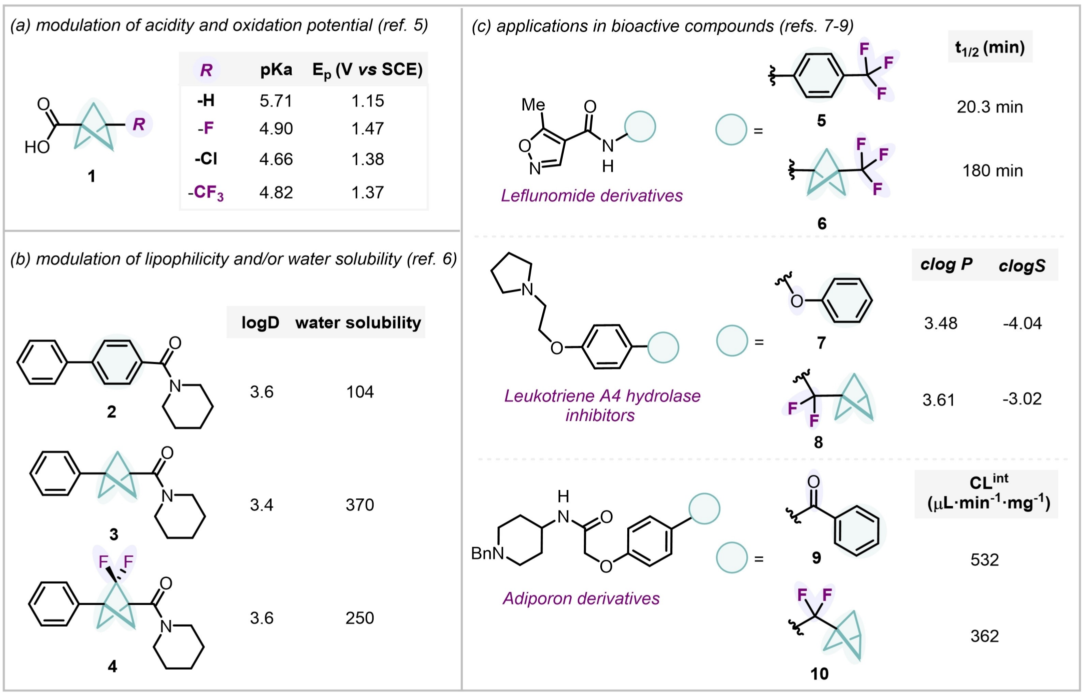


Figure 1. Selected studies and applications of fluorinated-BCPs.

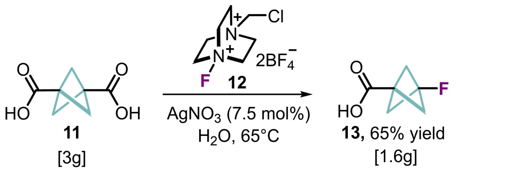


Figure 2. First example of a gram-scale synthesis of a F-containing BCP product **13**. *(ref [10])*.

13 (65% yield in gram scale), avoiding the need for chromatographic purification.[11]

Several strategies for synthesizing a diverse range of F-containing 1,3-disubstituted BCPs have been developed over the years, leveraging the strain-release reactivity of [1.1.1]-propellane **14** (Figure 3).[12] One of the earliest examples of preparing CF_3-containing BCP scaffolds was described by Adcock and Gakh in 1992, involving the reaction of CF_3I **15** with **14** (Figure 3a).[13] This method has since been adopted by other

Simone Baldon obtained his Master's degree cum laude in Chemistry from the University of Padova (Italy) in 2023. He then started his doctoral studies in the group of Prof. Luca Dell'Amico at the same university. His research focuses on the synthesis of new classes of organophotocatalysts for application to fine chemistry.

Luca Dell'Amico completed his PhD at the University of Parma (Italy), under the supervision of Prof. Franca Zanardi. He was visitng researcher with Prof. Karl Anker Jørgensen at Århus University (Denmark). In 2014, he was a Marie Curie COFUND fellow with Prof. Paolo Melchiorre at ICIQ (Spain). In 2017, he started his independent career as an assistant professor at the University of Padova. In 2019, was awarded the Giacomo Ciamician Medal from the Italian Chemical Society. Luca was promoted Associate Professor in 2022 and received the national scientific habilitation to full professor in 2023. In 2022, he was awarded an ERC starting grant to investigate new mechanistic pathways in organophotoredox catalysis. His research targets the development and mechanistic understanding of novel photochemical processes.

Sara Cuadros received her BSc from the University of Alicante (Spain) with disctinction (2014). She then obtained her M.Sc. and Ph.D. degrees working in the field of enantioselective photochemistry under the supervision of Prof. Paolo Melchiorre at the ICIQ (Tarragona, Spain). She also joined the group of Prof. Takashi Ooi at Nagoya University (Japan) as a visiting PhD student. In 2020, she moved to Padova University (Italy) as a postodctoral researcher in the group of Prof. Dell'Amico. Her research focuses on the development of organophotocatalyzed processes for the synthesis of medicinally relevant scaffolds.

Concept
doi.org/10.1002/ejoc.202400604

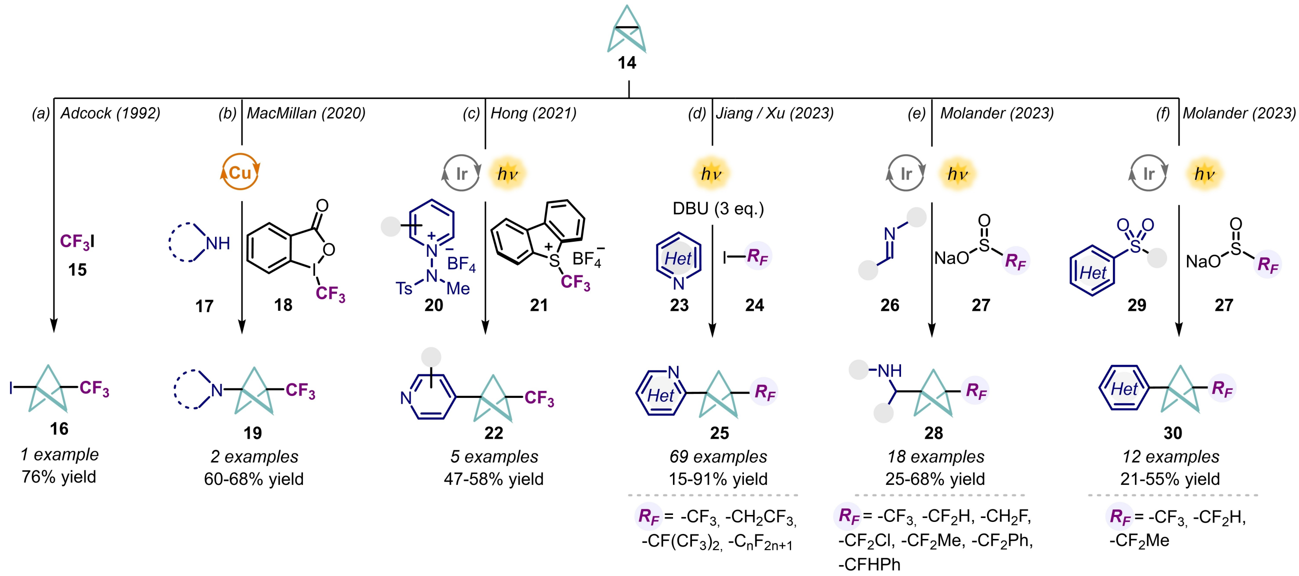


Figure 3. Strategies for the synthesis of fluoroalkyl 1,3-substituted BCPs.

research groups for the gram-scale production of the versatile product **16**.[14]

The fields of photochemistry and photocatalysis have offered practical approaches for generating a variety of perfluoroalkyl radicals, which can then be utilized in radical addition processes with [1.1.1]-propellane **14**. In 2020, the group of MacMillan reported a dual photoredox/copper-catalyzed three-component radical coupling between alkyl radicals, propellane **14** and heteroatom-based nucleophiles **17** (Figure 3b).[7] The scope of this transformation proved to be very general, affording 58 examples in 33–85% yield. Among these, two examples were reported using the Togni II reagent **18** as precursor of trifluoromethyl radicals, thus affording the corresponding flurorinated BCP products **19** in 60–68% yield. In contrast to the other alkyl radical precursors that were used in the scope, the reaction using **18** could be conducted without the necessity for photocatalyst and light irradiation.

One of the products **19** was then used in the synthesis of the analogue of *Leflunomide* **6** (see Figure 1c), which exhibited an increased metabolic stability in both rat and human liver microsomes in comparison with the original parent drug **5**.

In 2021, Hong and co-workers reported a photochemical strategy for the synthesis of a wide variety of 1,3-aminopyridyl-functionalizated BCPs, using *N*-aminopyridinium salts **20** as radical sources.[15] Interestingly, the applicability of the method was extended to the trifluoromethylative pyridylation of propellane **14** by using the Umemoto reagent **21** as source of trifluoromethyl radicals (Figure 3c). Although the reaction could be promoted *via* the formation of electron donor-acceptor (EDA) complexes[16] between **20** and NaOAc, the authors observed improved results with the use $Ir(ppy)_3$ as external photocatalyst. Five examples of this fluorination reaction were reported, including the use of complex pyridine-containing drugs, such as *vismodegib* and *bisacodyl*.

The works of MacMillan and Hong paved the way for the further exploration of other general three-component coupling reactions that allow the introduction of diverse fluoroalkyl moieties in the bridgehead positions of the BCP core. In 2023, the groups of Jiang and Xu simultaneously reported a general method to access a wide variety of perfluoroalkyl-substituted BCP derivatives **25**, under mild and metal-free reaction conditions (Figure 3d).[17] This transformation was triggered by light excitation of EDA-complexes generated upon association of perfluoroalkyl iodides **24** with 1,8-diazabiciclo[5.4.0]undeca-7-eno (DBU). Both methods proved to proceed in good yields with *N*-heterocyclic traps of different nature, as well as with perfluoroalkyl chains ranging from the simplest $-CF_3$ to long-chain perfluoroalkyl groups.

On the other hand, the group of Molander have provided diverse photocatalytic strategies to introduce fluoroalkyl groups on the BCP core, capitalizing on the use of fluoroalkylsulfinate salts **27** as source of fluoroalkyl radicals (Figure 3e and f).[18] In these transformations, a single electron transfer (SET) oxidation of **27** by an excited Ir photocatalyst generates the corresponding fluoroalkyl radicals, which rapidly engage in a radical addition process to the propellane **14**. Such event produces a BCP radical that can be successfully trapped with acceptors such as imines derivatives **26** (Figure 3e)[18a] and heteroaryl sulfones **29** (Figure 3f),[18b] thus yielding the corresponding fluorinated 1,3-disubstituted BCP products **28** and **30**.

The difluoromethylene group ($-CF_2-$) has been shown to act as an effective bioisostere of carbonyl groups (C=O), oxygen atoms or sulfonyl groups.[4] The combination of difluoroalkyl motifs ($-CF_2R$) with BCPs gives access to new Fsp^3-rich isosteric units, which can be potentially used as structural surrogates of aryl ethers and aryl ketones. In 2022, Gutierrez and co-workers reported a multicomponent cross coupling reaction from (fluoro)alkyl halides **31**, [1.1.1]propellane **14** and Grignard reagents **32**, using $Fe(acac)_3$ as pre-catalyst (Figure 4a).[19] The

Concept
doi.org/10.1002/ejoc.202400604

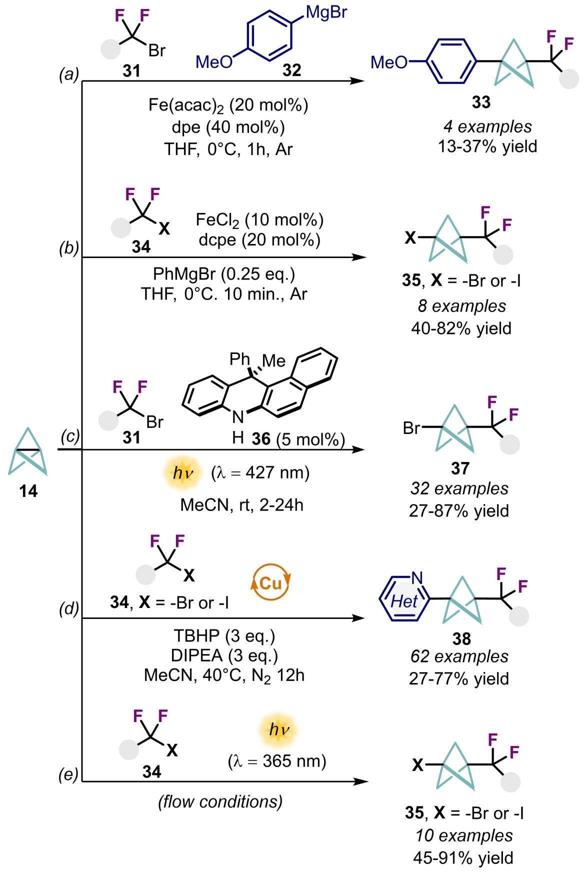


Figure 4. Strategies for the synthesis of difluoroalkyl 1,3-substituted BCPs. dpe: 1,2-dipiperidinoethane ; dcpe: 1,2-bis(dicyclohexylphosphino)ethane.

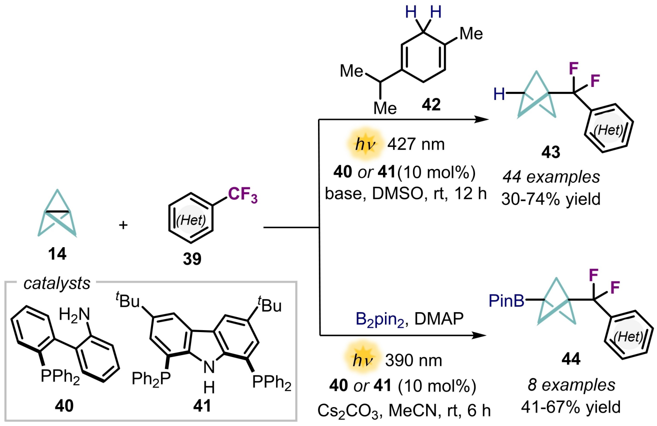


Figure 5. Photochemical synthesis of aryl difluoromethyl 1,3-substituted BCPs through C–F bond activation.

authors used both diamine and bisphosphine-based ligands, showing similar performance for the formation of the desired products. During this study, it was observed that together with the coupling product **33**, small amounts of the 1,3- alkyl BCP iodide **35** were also formed (Figure 4b). This reactivity was attributed to a Fe-catalyzed atom transfer radical addition ATRA process, which was further optimized, identifying $FeCl_2$ and 1,2-bis(dicyclohexylphosphino)ethane (dcpe) as the optimal catalytic system to trigger this alternative pathway. Under these conditions, 8 examples of the corresponding BCP halides **35** were obtained with good to excellent yields (40–82 % yield).

A general photochemical approach to difluoroalkyl BCPs was later developed by Dell'Amico's group in 2023 (Figure 4c).[8] This process uses 5 mol% of the dihydrobenzoacridine photocatalyst **36**, which upon light-excitation, promotes the generation of difluoroalkyl radicals, either by direct reduction of **31** or *via* an EDA-complex manifold between **36** and the substrate **31**. The difluoroalkyl radicals were then engaged in ATRA processes with the propellane **14** affording the corresponding bromo-substituted BCP products **37** in moderate to good yields (32 examples, 27–87 % yield). In addition, the authors synthesized the analogue of a LTA_4 hydrolase inhibitor **8** (see Figure 1c), replacing the original aryl ether moiety in **7** with the CF_2-BCP unit.[20] Noteworthy, the computed cLogP and cLogS values indicated an enhanced lipophilicity and water solubility of the new analogue **8**.

Xu and coworkers provided a copper-catalyzed method for obtaining a large variety of 1-haloalkyl-3-heteroaryl BCPs **38** (Figure 4d).[21] The key difluoroalkyl radicals were generated *via* a halogen atom transfer (XAT) process involving the organic halide precursor **34** and an α-aminoalkyl radical initially formed through a hydrogen atom transfer (HAT) process from DIPEA. One of the advantages of this method is the possibility of using primary, secondary and tertiary carbon radicals, thereby overcoming limitations encountered in previous methodologies, which were only effective with tertiary radicals.[19,22]

In 2023, the group of Mykhailiuk reported a continuous-flow method for synthesizing a large library of iodo-BCPs using a light-promoted reaction between alkyl iodides and propellane **14** (Figure 4e).[23] This scalable and practical approach does not require additional additives or catalysts and allows for the production of the target compounds in milligrams to kilogram quantities. Among the over 300 examples provided, 10 examples involved the synthesis of difluoroalkyl BCPs **35**, from the corresponding difluoroalkyl halides **34**.

In 2023, the group of Zhang introduced an alternative photochemical approach based in the activation of C–F bonds within trifluoromethylarenes **39** (Figure 5).[9] This strategy harnessed the *N*-anionic based organophotocatalyts **40** and **41**, which exhibited high efficacy in reducing **39** while generating the corresponding difluorobenzyl radicals. The addition of these radicals to [1.1.1]propellane **14** generates BCP radical intermediates that were subsequently engaged in hydrogen atom transfer processes to form **43**, or intercepted by B_2pin_2 to yield BCP-boronate products **44**. Remarkably, this transformation was applied to numerous aryl and heteroaryl trifluoromethyl derivatives, including complex bioactive substrates. Finally, the authors synthesized an analogue of the adiponectin receptor agonist *Adiporon* (**10** in Figure 1c). *In vitro* studies revealed a significant enhancement in the metabolic stability of the new analogue **10**, characterized by reduced clearance rates in human liver microsomes.

Concept
doi.org/10.1002/ejoc.202400604
Chemistry Europe
European Chemical Societies Publishing

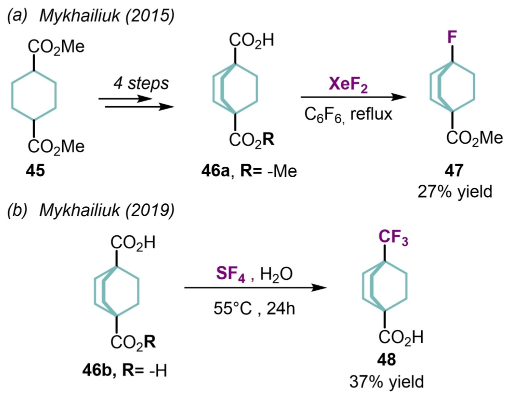


Figure 6. Synthesis of fluorinated bicyclo[2.2.2]octane derivatives.

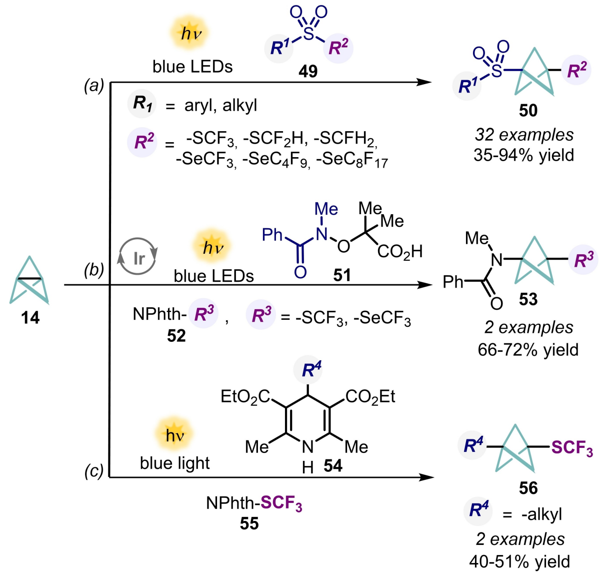


Figure 7. Strategies for the synthesis of fluoro-sulfur and fluoro-selenium 1,3-substituted BCPs. Phth: phthalimide.

Bicyclo[2.2.2]octane derivatives represent another class of saturated arene isosteres, which have garnered significant interest in drug discovery, medicinal chemistry and supramolecular chemistry over the past last decade.[12d] Compared to fluorinated BCPs, the synthesis of F-containing bicyclo[2.2.2]octanes has been less explored. In 2015, Mykhailiuk's group reported a strategy to synthesize the versatile monofluoro-substituted compound **47** (Figure 6a).[24a] This approach involved a 4-step synthesis of the carboxylic acid **46a**, which was subsequently converted into compound **47** using xenon difluoride (XeF_2) as the fluorinating agent. Additionally, the same group synthesized the CF_3 derivative **48** from the dicarboxylic acid **46b**, using sulfur tetrafluoride (SF_4) in presence of water as fluorinating agent (Figure 6b).[24b]

2.2. Introduction of Fluorosulfur, Fluoroselenium (–SFx, –SeFx) and their Fluoralkyl Derivatives (–SR_F, –SeR_F)

The synergistic coupling of fluorine and fluoroalkyl moieties with chalcogen atoms has recently garnered considerable attention in pharmaceutical and agrochemical research. This alliance offers a promising avenue for imparting distinctive physicochemical properties to small organic molecules, characterized by augmented electron-withdrawing character along with high lipophilicity.[25] Several strategies have been developed to incorporate these emerging functionalities into the structure of BCPs.

In 2020, Zhu and co-workers developed one of the first general protocols for the synthesis of fluoroalkylthio- and fluoroalkylseleno-functionalized BCPs **50** (Figure 7a).[26] Based on different mechanistic studies, including electrospin paramagnetic resonance (EPR), the authors proposed as the initiation step the homolysis of the strained C–C bond of [1.1.1]propellane **14**, promoted by thermal activation or light irradiation. The corresponding BCP diradical reacts with the S–R^2 bond of reagent **49**, leading to the generation of a sulfone radical (R^1–$SO_2^•$) together with a monofunctionalized BCP radical (R^2–BCP•), which then recombine to afford the final product **50**. The reaction shows excellent tolerance towards aryl and alkyl-substituted sulfones **49**. In addition, several thiofluorinated and selenofluorinated groups were efficiently incorporated with excellent yields, such as –SCF_3, –SCF_2H, –SFH_2, –$SeCF_3$ and Se-perfluoroalkyl moieties, under mild reaction conditions, 100% atom economy and good process scalability.

The same year, Leonori, Sheikh and coworkers developed a light-driven amino-functionalization process of propellane **14**, using amidyl radical precurors **51** together with different type of SOMOphiles (Figure 7b). Two examples were reported with the phthalimide-based reagents **52** as effective SOMOphilic reagents, which allowed the introduction of the –SCF_3 and $SeCF_3$ functionalities in the BCP core.[27] On the other hand, the group of Molander provided two examples of photochemical trifluoromethylthiolation of **14**, capitalizing on the ability of 1,4-dihydropyridines **54** to engage in EDA-complex formation with the SCF_3-substituted phthalimide **55** (Figure 7c).[28]

In 2022, a collaboration between Cornella, Pitts and co-workers led to the development of a synthetic protocol for the mild radical pentafluorosulfanylation and tetrafluoro(aryl)sulfanylation of [1.1.1]propellane **14**, thus accessing to the isosteric hybrids BCP–SF_5 chloride **57** and BCP–SF_4Ar chloride **58** (Figure 8a).[29] The SF_5–BCP–Cl derivative **57** is formed *via* an ATRA mechanism, which is initiated through the photoexcitation of the SF_5Cl reagent (used as a gas solution in hexane). In the case of the formation of the $ArSF_4$–BCP–Cl derivative **58**, the reaction between $ArSF_4Cl$ and **14** occurs spontaneously in the dark at –45 °C, also *via* a radical-chain ATRA process.

In 2023, Qing and co-workers reported a variation of the Cornella-Pitts work that allows the synthesis of the SF_5–BCP–I iodide **59** *via* a three-component iodopentafluorosulfanylation reaction between SF_5Cl, propellane **14** and CH_2I_2 (Figure 8b).[30] The process was initiated by thermal homolysis of the S–Cl bond within SF_5Cl, which occurs at ambient temperature. The generated SF_5 radical rapidly adds on the [1.1.1]propellane **14**

Concept
doi.org/10.1002/ejoc.202400604

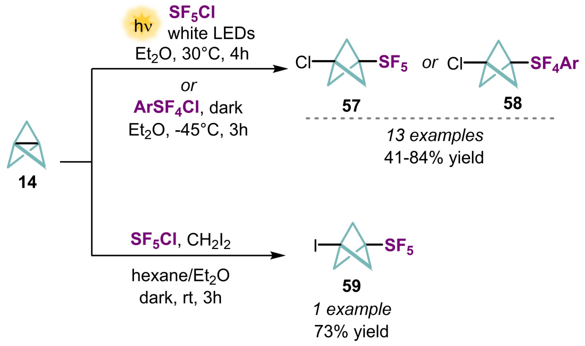
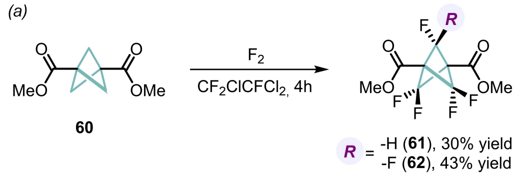
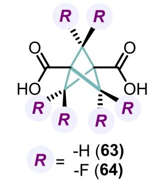


Figure 8. Synthesis of $-SF_5$ and $-SF_4Ar$ substituted BCPs.





R	pKa_1	pKa_2
-H	3.22	4.26
-F	0.73	1.34

Figure 9. (a) First example of fluorination of the BCP structure, reported by Michl's group (ref. [32a]); (b) Comparison of the acidity of compound **64** with its non-fluorinated analogue **63**.

to generate a BCP radical that preferentially undergoes halogen atom transfer (XAT) with CH_2I_2, rather than with the starting substrate SF_5Cl. The reaction proceeds efficiently even in gram-scale (10 mmol scale, 73 % yield) and with minimal formation of the alternative ATRA product SF_5–BCP–Cl **57**. Importantly, the iodide BCP product **59** was easily functionalized *via* single electron reduction of the C–I bond, thus generating a BCP radical that was subsequently engaged in radical addition processes to alkenes or disulfides. Qing's contribution provided a solution related to the nature of the SF_5–BCP–Cl products **59** formed with the Cornella-Pitts protocol. Indeed, the BCP chloride derivatives are difficult to further functionalize *via* C–Cl bond activation, while BCP iodides have demonstrated their ability to participate in a variety of radical-based and polar transformations,[31] thus allowing the synthesis of more complex SF_5–BCP derivatives.

3. Bridge Functionalization

3.1. Introduction of Fluorine Atoms

The direct installation of fluorine or fluoroalkyl substituents at the bridge (2,4,5) positions of the BCP scaffold is a formidable challenge for which general methodology remains largely underdeveloped. The first attempts to this goal dates back to 1997, when Michl's group succeeded in synthesizing dimethyl pentafluorobicyclo[1.1.1]pentane-1,3-dicarboxylate **61** and dimethyl hexafluorobicyclo[1.1.1]pentane-1,3-dicarboxylate **62** (Figure 9a).[32a] These two products could be obtained by gas-phase fluorination of dimethyl bicyclo[1.1.1]pentane-1,3-dicarboxylate **60**. Subsequent studies revealed the interesting influence that the presence of fluorine has on both the geometry and the physicochemical properties of the di-carboxylic acid **64**, compared to its non-fluorinated analogue **63** (Figure 9b). For example, from the pKa analyses in aqueous solution, it was shown that the hexafluorinated di-carboxylic derivative **64** has an acidity up to 2.55 points lower than the defluorinated analogue **63**.

In 2019, the group of Ma and Mykhailiuk developed independently a synthetic protocol for the synthesis of 2,2-difluoro-BCPs derivatives ("BCP-F_2", **67**), *via* the addition of difluorocarbene (:CF_2) to bicyclo[1.1.0]butane **65** (Figure 10a and b).[6,33] In the methodology of Ma, difluorocarbene was generated from trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate (TFDA, **66**) at 90 °C in the presence of substoichiometric amounts of NaF as initiator,[33] while Mykhailiuk's method employs a large excess of CF_3TMS at 70 °C, using NaI as initiator.[6] Both processes proceed in good yields, but are limited to the synthesis of 1-phenyl-3-ester-substituted BCPs, with only one example yielding a 1-vinyl-3-ester substituted BCP product. Additionally, both works provided an analysis on

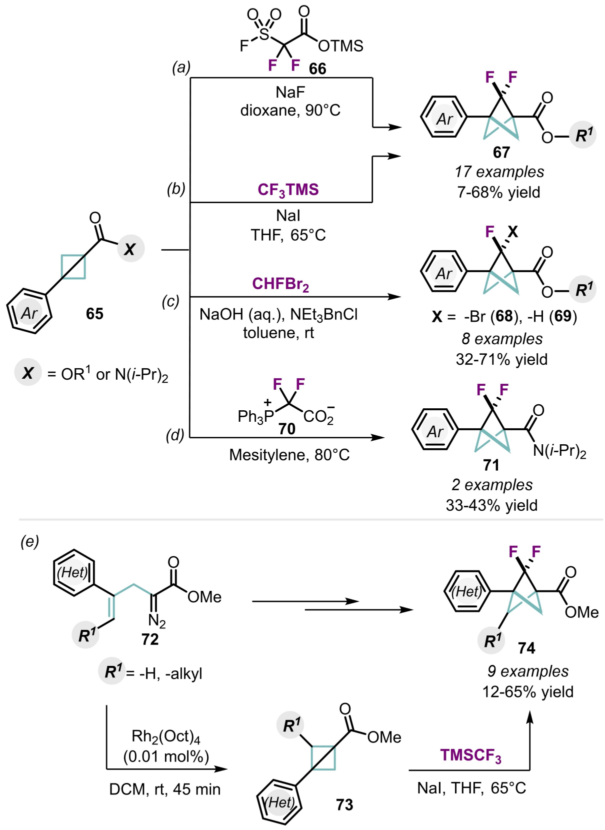


Figure 10. Synthetic strategies towards 2,2-difluoro and 2-monofluoro substituted BCPs (BCP–F_2 and BCP–F).

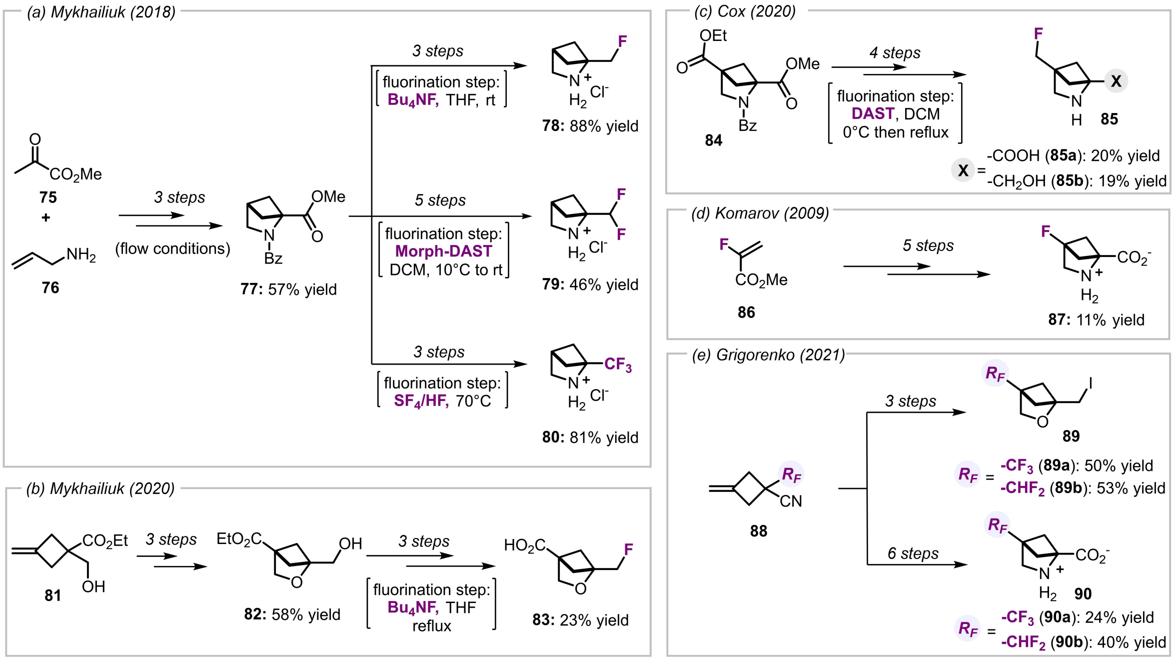


Figure 11. Multi-step strategies for the synthesis of fluorinated 2-azabicyclo[2.1.1]hexane and 2-oxabicyclo[2.1.1]hexane derivatives. Yields refer to overall yield.

the acidity, basicity, lipophilicity, and water solubility of some BCP–F_2 derivatives, in comparison with their non fluorinated BCP analogues (selected example in Figure 1b). Subsequent works by Ma and other groups have described further functionalization of the BCP–F_2 products **67**, thus allowing the diversification of these molecules into more complex substrates.[34]

Some years later, in 2022, Mykhailiuk and co-workers published the first scalable route for the synthesis of 2-fluoro substituted BCPs **69**, *via* the addition of the bromofluorocarbene (:CBrF) on **65** (Figure 10c).[35] The process was triggered at room temperature treating the carbene precursor $CHFBr_2$ with NEt_3BnCl in toluene, and an aqueous solution of NaOH. The reaction of the corresponding bromide **68** with freshly prepared Raney nickel in the presence of ethylenediammine (EDA), yielded the desired mono-fluorinated BCP **69** in up to 96% yield.

Other difluorocarbene precursors, such as the zwitterionic phosphonium carboxylates **70** developed by Anderson's group, have also been successfully used to synthesize BCP amide derivatives **71** starting from bicyclo[1.1.0]butane **65** (Figure 10d).[36]

In 2023, the group of Davies reported a rhodium-catalyzed approach to access a variety of 3-(hetero)arylbicyclo[1.1.0]butanes **73**, using the modular α-allyldiazoacetates **72** as precursors (Figure 10e).[37] The bicyclobutanes were then directly use in the one-pot synthesis of densely functionalized BCP–F_2 products **74**, capitalizing on the previously described Mykhailiuk's group protocol. The Davies' work allows the expansion of the BCP–F_2 products **74** that can be accessed with the difluorocarbene chemistry, including examples bearing polyaromatic and heteroaromatic groups in the bridgehead positions of the BCP–F_2 core.

4. Synthesis of F-containing Bridged Hetero-bicycles

Different groups have recently provided multi-step strategies for building-up F-containing bridged heterobicyclic structures (Figures 11 and 12).[38–45] A particular emphasis has been putted in the synthesis of 2,4-methanoproline fluorinated derivatives (**78–80**, **85**, **87**, **90**), and its oxa-analogues (**83**, **89**) for which several gram-scale routes have been successfully developed

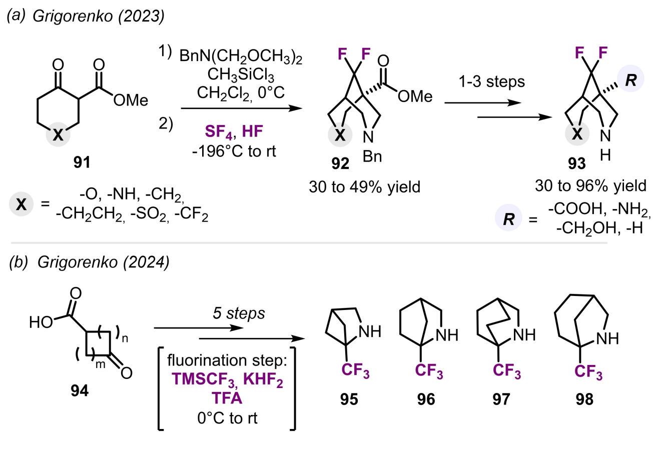


Figure 12. Synthetic strategies for the preparation of fluoro-substituted hetero-bicyclic compounds.

(Figure 11).[38–43] 2,4-methanoproline is a naturally-occurring non-proteinogenic amino acid that is considered a highly valuable building block in medicinal chemistry, since it can be used as proline analogue.[46] The approaches to accessing these substrates involve either performing a fluorination step after constructing the desired bridged bicyclic structure (examples a–c), or starting the synthetic route with F-containing starting materials (examples d–e).

In 2018, Mykhailiuk's group successfully implemented a gram-scale synthesis of the 2,4-methaneproline **77** derivative using a continuous flow process, starting from commercially available and cost-effective substrates, such as methyl 2-oxopropanoate **75** and allylamine **76** (Figure 11a).[38] Various structural modifications were subsequently performed to yield the monofluoromethyl, difluoromethyl, and trifluoromethyl derivatives (**78**–**80**) in good to excellent yields (46–88%). Subsequently, the same group developed a protocol for the synthesis of oxabicyclo[2.1.1]hexane derivatives through a multistep process, beginning with the ring closure of the starting material (3-methylenecyclobutyl)methanol **81** (Figure 11b).[39] The alcohol **82** was then converted to the corresponding monofluoromethyl derivative **83** using tetrabutyl ammonium fluoride (Bu_4NF) as the fluorinating agent.

Another example of fluorination of heterobicyclic compounds was reported by Cox *et. al.* (Figure 11c), who synthesized the two monofluoromethyl derivatives of azabicyclo[2.1.1]hexane **85 a–b** *via* fluorination of the diester **84** with (diethylamino)sulfur trifluoride (DAST).[40]

Regarding the approaches using fluorinated starting materials, Komarov's group reported in 2009 the synthesis of the 4-fluoro-2-azabicyclo[2.1.1]hexane derivative **87**, in 5 steps from the commercially available compound **86** (Figure 11d).[41a] The desired product was obtained with a yield as low as 11%. More recently, Grigorenko's group developed two different synthetic routes for the synthesis of trifluoromethyl and difluoromethyl derivatives of 2-oxabicyclo[2.1.1]hexane (**89 a–b**), as well as for the 2-azabicyclo[2.1.1]hexanes **90 a–b** (Figure 11e).[42] These products can be obtained from the corresponding starting material **88** in moderate yields (24–53%). The synthesis of related products, featuring the R_F groups at the bridge 3-position of the 2-oxabicyclo[2.1.1]hexane core, has recently been described by the Mykhailiuk group.[43]

In 2023, Grigorenko's group developed a general methodology for the preparation of an extended class of gem-difluoro-3-azabicyclo[3.n.1]alkanes **93**, which can be considered as conformationally-restricted analogues of piperidine, one of the most common heterocyclic scaffolds used in drug discovery (Figure 12a).[44] These complex compounds are initially prepared through double-Mannich addition/annulation process from β-ketoesters **91**, followed by a deoxofluorination with SF_4 and HF at −196 °C. The generality of the process was very broad, including the synthesis of fluorinated piperidine derivatives containing additional heteroatoms in the bicyclic core, as well as other heterobicycles **93** containing substituents that can be engaged in further functionalization processes.

In 2024 the same group developed the multi-step synthesis of α-CF_3-substituted saturated bicyclic amines **95–98** from commercial cyclic ketones **94** (Figure 12b).[45] Different sized bicyclic amines (**95**–**98**) were obtained in gram scale and good yields, *via* the addition of the Ruppert-Prakash reagent to an *in-situ* generated imine from **94**, followed by a $AlMe_3$-promoted intramolecular heterocyclization, as key steps. In addition, analysis of parameters such as basicity and lipophilicity allowed to determine the influence of the $-CF_3$ substituent on the chemical and physical properties of the molecule.

5. Summary and Outlook

Over the last years, the synthesis of BBCs has garnered increasing attention due to their important applications in medicinal chemistry, catalysis, and materials science as versatile 3D-replacements for planar arene rings. The incorporation of fluorine atoms and fluoroalkyl groups into these molecular frameworks leads to the creation of hybrid 3D-structures with distinct physicochemical properties compared to their non-fluorinated counterparts. A significant progress has been made in the synthesis of F-containing BCPs. The primary strategy for introducing fluorinated moieties into the bridgehead (1,3) positions of this bicycloalkane have involved the photocatalytic generation of fluoroalkyl radicals, which readily undergo addition to the strained σ-bond of [1.1.1]-propellane. However, strategies for substitution of the bridge (2,4,5) positions have been comparatively underdeveloped. The current few methods rely on the reaction of difluorocarbenes, generated from various precursors under thermal conditions, with the strained σ-bond of bicyclobutanes.

On the other hand, fluorinated chalcogen-based functional groups, including $-SR_F$, $-SeR_F$, $-SF_5$, or $-SF_4Ar$, have been effectively incorporated into BCPs primarily through photocatalytic strategies. However, these approaches exhibit limited versatility, prompting the need for expanded protocols facilitating the simultaneous introduction of diverse groups alongside with F-chalcogen functionalities at the bridgehead or bridge positions.

Current strategies for synthesizing F-containing bridged hetero-bicycles, predominantly involve multistep procedures, which restrict their synthetic versatility. Consequently, the development of direct methods for the selective introduction of F-containing motifs at different positions of the bicyclic core, would be highly desirable.

Although substantial research has focused on BCP frameworks, we anticipate the development of additional strategies for incorporating fluorine or fluorinated groups into other significant BBCs, such as bicyclo[2.1.1]hexanes, bicyclo[3.1.1]heptanes, bicyclo[2.2.2]octane and their heterobicyclic variants.[47] These scaffolds have already been validated as 3D-surrogates for non- linear arene rings.

Advancing new methods to overcome current challenges in the synthesis of F-containing BBCs opens new opportunities for exploring 3D-chemical space across different research fields. This progress offers exciting prospects for developing the next generation of pharmaceuticals, materials or catalysts with refined properties.

Acknowledgements

L.D acknowledges Ministero dell'Università (PRIN 2020927WY3 002), and the European Research Council (ERC-Starting Grant 2021 SYNPHOCAT 101040025 for financial support. Open Access publishing facilitated by Università degli Studi di Padova, as part of the Wiley - CRUI-CARE agreement.

Conflict of Interests

The authors declare no conflict of interest.

Keywords: Fluorinated isosteres · Bicycloalkanes · Bridged bicyclic compounds · Synthetic methods.

[1] a) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591; b) N. A. Meanwell, *Chem. Res. Toxicol.* **2016**, *29*, 564–616; c) E. G. Tse, S. D. Houston, C. M. Williams, G. P. Savage, L. M. Rendina, I. Hallyburton, M. Anderson, R. Sharma, G. S. Walker, R. S. Obach, M. H. Todd, *J. Med. Chem.* **2020**, *63*, 11585–11601; d) N. A. Meanwell, *J. Agric. Food Chem.* **2023**, *71*(47), 18087–18122.
[2] a) P. K. Mykhailiuk, *Org. Biomol. Chem.* **2019**, *17*, 2839–2849; b) M. A. M. Subbaiah, N. A. Meanwell, *J. Med. Chem.* **2021**, *64*(19), 14046–14128.
[3] a) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*(21), 8315–8359; c) S. Swallow, *Prog. Med. Chem.* **2015**, *54*, 65–133.
[4] a) N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880; b) S. Meyer, J. Häfliger, R. Gilmour, *Chem. Sci.* **2021**, *12*, 10686–10695.
[5] W. Adcock, A. V. Blokhin, G. M. Elsey, N. H. Head, A. R. Krstic, M. D. Levin, J. Michl, J. Munton, E. Pinkhassik, M. Robert, J.-M. Savéant, A. Shtarev, I. Stibor, *J. Org. Chem.* **1999**, *64*(8), 2618–2625.
[6] R. M. Bychek, V. Hutskalova, Y. P. Bas, O. A. Zaporozhets, S. Zozulya, V. V. Levterov, P. K. Mykhailiuk, *J. Org. Chem.* **2019**, *84*(23), 15106–15117.
[7] X. Zhang, R. T. Smith, C. Le, S. J. McCarver, B. T. Shireman, N. I. Carruthers, D. W. C. MacMillan, *Nature* **2020**, *580*, 220–226.
[8] S. Cuadros, G. Goti, G. Barison, A. Raulli, T. Bortolato, G. Pelosi, P. Costa, L. Dell'Amico, *Angew. Chem. Int. Ed.* **2023**, *62*, e202303585.
[9] M. Chen, Y. Cui, X. Chen, R. Shang, X. Zhang, *Nat. Commun.* **2024**, *15*, 419–428.
[10] Y. L. Goh, V. A. Adsool, *Org. Biomol. Chem.* **2015**, *13*, 11597–11601.
[11] a) S. O. Kokhan, A. V. Tymtsunik, S. L. Grage, S. Afonin, O. Babii, M. Berditsch, A. V. Strizhak, D. Bandak, M. O. Platonov, I. V. Komarov, A. S. Ulrich, P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2016**, *55*, 14788–14792; b) V. Ripenko, D. Vysochyn, I. Klymov, S. Zhersh, P. K. Mykhailiuk, *J. Org. Chem.* **2021**, *86*(20), 14061–14068.
[12] a) J. Turkowska, J. Durka, D. Gryko, *Chem. Commun.* **2020**, *56*, 5718–5734; b) P. Bellotti, F. Glorius, *J. Am. Chem. Soc.* **2023**, *145*, 20716–20732; c) B. R. Shire, E. A. Anderson, *JACS Au* **2023**, *3*(6), 1539–1553; d) S. Cuadros, J. Paut, E. Anselmi, G. Dagousset, E. Magnier, L. Dell'Amico, *Angew. Chem. Int. Ed.* **2024**, *63*, e2023173335.
[13] J. L. Adcock, A. A. Gakh, *J. Org. Chem.* **1992**, *57*, 6206–6210.
[14] a) P. K. Mikhailiuk, S. Afonin, A. N. Chernega, E. B. Rusanov, M. O. Platonov, G. G. Dubinina, M. Berditsch, A. S. Ulrich, I. V. Komarov, *Angew. Chem. Int. Ed.* **2006**, *45*, 5659–5661; b) P. K. Mykhailiuk, N. M. Voievoda, S. Afonin, A. S. Ulrich, I. V. Komarov, *J. Fluorine Chem.* **2010**, *131*, 217–220.
[15] S. Shin, S. Lee, W. Choi, N. Kim, S. Hong, *Angew. Chem. Int. Ed.* **2021**, *60*, 7873–7879.
[16] C. G. S. Lima, T. M. Lima, M. Duarte, I. D. Jurberg, M. W. Paixão, *ACS Catal.* **2016**, *6*(3), 1389–1407.
[17] a) B. Yan, G. Xu, H. Han, J. Hong, W. Xu, D. Lan, C. Yu, X. Jiang, *Green Chem.* **2023**, *25*, 1948–1954; b) J. Zhu, Y. Guo, Y. Zhang, W. Li, P. Zhang, Jun Xu, *Green Chem.* **2023**, *25*, 986–992.
[18] a) W. Huang, Y. Zheng, S. Keess, G. A. Molander, *J. Am. Chem. Soc.* **2023**, *145*, 5363–5369; b) W. Huang, S. Keess, G. A. Molander, *Angew. Chem. Int. Ed.* **2023**, *62*, e202302223.
[19] A. Rentería-Gómez, W. Lee, S. Yin, M. Davis, A. R. Gogoi, O. Gutierrez, *ACS Catal.* **2022**, *12*, 11547–11556.
[20] T. D. Penning, N. S. Chandrakumar, B. B. Chen, H. Y. Chen, B. N. Desai, S. W. Djuric, S. H. Docter, A. F. Gasiecki, R. A. Haack, J. M. Miyashiro, M. A. Russell, S. S. Yu, D. G. Corley, R. C. Durley, B. F. Kilpatrick, B. L. Parnas, L. J. Askonas, J. K. Gierse, E. I. Harding, M. K. Highkin, J. F. Kachur, S. H. Kim, G. G. Krivi, D. Villani-Price, E. Y. Pyla, W. G. Smith, *J. Med. Chem.* **2000**, *43*(4), 721–735.
[21] Y. Guo, J. Zhu, Y. Wang, Y. Li, H. Hu, P. Zhang, J. Xu, W. Li, *ACS Catal.* **2024**, *14*, 619627.
[22] W. Huang, S. Keess, G. Molander, *J. Am. Chem. Soc.* **2022**, *144*, 1296112969.
[23] V. Ripenko, V. Sham, V. Levchenko, S. Holovchuk, D. Vysochyn, I. Klymov, D. Kyslyi, S. Veselovych, S. Zhersh, Y. Dmytriv, A. Tolmachov, I. Sadkova, I. Pishel, P. Mykhailiuk, *ChemRxiv* **2023**, DOI: 10.26434/chemrxiv-2023-8dclm.
[24] a) D. Bandak, O. Babii, R. Vasiuta, I. V. Komarov, P. K. Mykhailiuk, *Org. Lett.* **2015**, *17*, 226–229; b) M. Bugera, S. Trofymchuk, K. Tarasenko, O. Zaporozhets, Y. Pustovit, P. K. Mykhailiuk, *J. Org. Chem.* **2019**, *84*, 16105–16115.
[25] a) X. H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731–764; b) A. Modak, E. N. Pinter, S. P. Cook, *J. Am. Chem. Soc.* **2019**, *141*, 18405–18410; c) E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 2832–2842.
[26] Z. Wu, Y. Xu, J. Liu, X. Wu, C. Zhu, *Sci. China Chem.* **2020**, *63*, 1025–1029.
[27] J. H. Kim, A. Ruffoni, Y. S. S. Al-Faiyz, N. S. Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* **2020**, *59*, 8225–8231.
[28] A. Lipp, S. O. Badir, R. Dykstra, O. Gutierrez, G. A. Molander, *Adv. Synth. Catal.* **2021**, *363*, 3507–3520.
[29] Y. Kraemer, C. Ghiazza, A. N. Ragan, S. Ni, S. Lutz, E. K. Neumann, J. C. Fettinger, N. Nöthling, R. Goddard, J. Cornella, C. Ross Pitts, *Angew. Chem. Int. Ed.* **2022**, *61*, e202211892.
[30] X. Zhao, J. Y. Shou, F. L. Quing, *Sci. China Chem.* **2023**, *66*, 2871–2877.
[31] a) D. F. J. Caputo, C. Arroniz, A. B. Dürr, J. J. Mousseau, A. F. Stepan, S. J. Mansfielda, E. A. Anderson, *Chem. Sci.* **2018**, *9*, 5295–5300; b) J. Nugent, C. Arroniz, B. R. Shire, A. J. Sterling, H. D. Pickford, M. L. J. Wong, S. J. Mansfield, D. F. J. Caputo, B. Owen, J. J. Mousseau, F. Duarte, E. A. Anderson, *ACS Catal.* **2019**, *9*, 9568–9574; c) J. Nugent, B. R. Shire, D. F. J. Caputo, H. D. Pickford, F. Nightingale, I. T. T. Houlsby, J. J. Mousseau, E. A. Anderson, *Angew. Chem. Int. Ed.* **2020**, *59*, 11866–11870; d) H. D. Pickford, J. Nugent, B. Owen, J. J. Mousseau, R. C. Smith, E. A. Anderson, *J. Am. Chem. Soc.* **2021**, *143*, 9729–9736; e) T. Constantin, B. Górski, M. J. Tilby, S. Chelli, F. Juliá, J. Llaveria, K. J. Gillen, H. Zipse, S. Lakhdar, D. Leonori, *Science* **2022**, *377*, 1323–1328.
[32] a) M. D. Levin, S. J. Hamrock, P. Kaszynski, A. B. Shtarev, G. A. Levina, B. C. Noll, M. E. Ashley, R. Newmark, G. G. I. Moore, J. Michl, *J. Am. Chem. Soc.* **1997**, *119*(52), 12750–12761; b) A. B. Shtarev, E. Pinkhassik, M. D. Levin, I. Stibor, J. Michl, *J. Am. Chem. Soc.* **2001**, *123*, 3484–3492.
[33] X. Ma, D. L. Sloman, Y. Han, D. Bennett, *Org. Lett.* **2019**, *21*, 7199–7203.
[34] a) X. Ma, W. Pinto, L. N. Pham, D. L. Sloman, Y. Han, *Eur. J. Org. Chem.* **2020**, 4581–4605; b) T. P. Le, I. Rončević, M. Dračínský, I. Císařová, V. Šolínová, V. Kašička, J. Kaleta, *J. Org. Chem.* **2021**, *86*, 10303–10319; c) X. Ma, C. S. Yeung, *J. Org. Chem.* **2021**, *86*, 10672–10698; d) X. Ma, J. L. Chen, B. E. Gaskins, *Org. Lett.* **2024**, *26*, 1947–1951.
[35] R. Bychek, P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205103.
[36] R. E. McNamee, M. M. Haugland, J. Nugent, R. Chan, K. E. Christensen, E. A. Anderson, *Chem. Sci.* **2021**, *12*, 7480–7485.
[37] J. C. Sharland, H. M. L. Davies, *Org. Lett.* **2023**, *25*, 5214–5219.
[38] V. V. Levterov, O. Michurin, P. O. Borysko, S. Zozulya, I. V. Sadkova, A. A. Tolmachev, P. K. Mykhailiuk, *J. Org. Chem.* **2018**, *83*(23), 14350–14361.
[39] V. V. Levterov, Y. Panasyuk, V. O. Pivnytska, P. K. Mykhailiuk, *Angew. Chem., Int. Ed.* **2020**, *59*, 7161–7167.
[40] B. Cox, V. Zdorichenko, P. B. Cox, K. I. Booker-Milburn, R. Paumier, L. D. Elliott, M. Robertson-Ralph, G. Bloomfield, *ACS Med. Chem. Lett.* **2020**, *11*(6), 1185–1190.
[41] a) A. N. Tkachenko, D. S. Radchenko, P. K. Mykhailiuk, O. O. Grygorenko, I. V. Komarov, *Org. Lett.* **2009**, *11*(24), 5674–5676; b) P. K. Mykhailiuk, V. Kubyshkin, T. Bach, N. Budisa, *J. Org. Chem.* **2017**, *82*, 8831–8841.
[42] A. A. Homon, O. V. Hryshchuk, O. V. Mykhailenko, B. V. Vashchenko, K. P. Melnykov, O. M. Michurin, C. G. Daniliuc, I. I. Gerus, V. O. Kovtunenko, I. S. Kondratov, O. O. Grygorenko, *Eur. J. Org. Chem.* **2021**, *2021*, 6580–6590.
[43] V. V. Levterov, Y. Panasiuk, O. Shablykin, O. Stashkevych, K. Sahun, A. Rassokhin, I. Sadkova, D. Lesyk, A. Anisiforova, Y. Holota, P. Borysko, I.

Bodenchuk, N. M. Voloshchuk, P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2024**, *63*, e202319831.

[44] S. Kihakh, K. P. Melnykov, V. Bilenko, S. Trofymchuk, O. S. Liashuk, O. O. Grygorenko, *Eur. J. Org. Chem.* **2023**, *27*, e202300937.

[45] O. Smyrnov, K. P. Melnykov, V. Semeno, O. S. Liashuk, O. O. Grygorenko, *Eur. J. Org. Chem.* **2024**, *27*, e202300935.

[46] a) C. Lescop, L. Mévellec, F. Huet, *J. Org. Chem.* **2001**, *66*, 4187–4193; b) C. L. Jenkins, G. Lin, J. Duo, D. Rapolu, I. A. Guzei, R. T. Raines, G. R. Krow, *J. Org. Chem.* **2004**, *69*, 8565–8573.

[47] a) E. W. Della, N. J. Head, *J. Org. Chem.* **1992**, *57*, 2850–2855; b) M. Reinhold, J. Steinebach, C. Golz, J. C. L. Walker, *Chem. Sci.* **2023**, *14*, 9885–9891; c) A. Denisenko, P. Garbuz, Y. Makovetska, O. Shablykin, D. Lesyk, G. Al-Maali, R. Korzh, I. V. Sadkova, P. K. Mykhailiuk, *Chem. Sci.* **2023**, *14*, 14092–14099; d) V. V. Levterov, Y. Panasiuk, K. Sahun, O. Stashkevych, V. Badlo, O. Shablykin, I. Sadkova, L. Bortnichuk, O. Klymenko-Ulianov, Y. Holota, L. Lachmann, P. Borysko, K. Horbatok, I. Bodenchuk, Y. Bas, D. Dudenko, P. K. Mykhailiuk, *Nat. Commun.* **2023**, *14*, 5608–5617.

Manuscript received: June 1, 2024
Revised manuscript received: August 2, 2024
Accepted manuscript online: August 5, 2024
Version of record online: October 30, 2024